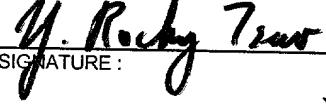


SUBSTITUTE FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 00537-184002
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If Known, see 37 CFR 1.5) 09/830945
INTERNATIONAL APPLICATION NO. US99/25706	INTERNATIONAL FILING DATE 2 November 1999	PRIORITY DATE CLAIMED 2 November 1998
TITLE OF INVENTION LACTONE BEARING ABSORBABLE POLYMERS		
APPLICANT(S) FOR DO/EO/US Francis X. Ignatious		
<p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)). 4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ul style="list-style-type: none"> a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ul style="list-style-type: none"> a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). 		
Items 11 to 16 below concern other documents or information included:		
<ol style="list-style-type: none"> 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input type="checkbox"/> Other items or information: <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 		
<div style="border: 1px solid black; padding: 5px;"> <p style="margin: 0;">CERTIFICATE OF MAILING BY EXPRESS MAIL</p> <p style="margin: 0;">Express Mail Label No. <u>EI 259011750 US</u></p> <p style="margin: 0;">I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D C 20231</p> <p style="margin: 0; font-size: small;">May 2, 2001</p> <p style="margin: 0; font-size: small;">Signature</p> <p style="margin: 0; font-size: small;">Date of Deposit</p> <p style="margin: 0; font-size: small;">Typed Name of Person Signing</p> <p style="margin: 0; font-size: small;">Samantha Bell Samantho Bell</p> </div>		

U.S. APPLICATION NO. (IF KNOWN) 097830945	INTERNATIONAL APPLICATION NO. US99/25706	ATTORNEY'S DOCKET NUMBER 00537-184002		
17. <input checked="" type="checkbox"/> The following fees are submitted:		CALCULATIONS PTO USE ONLY		
Basic National Fee (37 CFR 1.492(a)(1)- (5)):				
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... \$1000				
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860				
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... \$710				
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... \$690				
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)..... \$100				
ENTER APPROPRIATE BASIC FEE AMOUNT =		\$860.00		
Surcharge of \$130 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$0.00		
Claims	Number Filed	Number Extra	Rate	
Total Claims	30 - 20 =	10	x \$18	\$180.00
Independent Claims	1 - 3 =		x \$80	\$0.00
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ \$270	\$0.00
TOTAL OF ABOVE CALCULATIONS =		\$0.00		
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.		\$0.00		
		SUBTOTAL =	\$1,040.00	
Processing fee of \$130 for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))		\$0.00		
		TOTAL NATIONAL FEE =	\$1,040.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +		\$0.00		
		TOTAL FEES ENCLOSED =	\$1,040.00	
		Amount to be refunded:	\$	
		Charged:	\$	
a. <input checked="" type="checkbox"/> A check in the amount of \$1040.00 to cover the above fees is enclosed.				
b. <input type="checkbox"/> Please charge my Deposit Account No. 06-1050 in the amount of \$0.00 to cover the above fees. A duplicate copy of this sheet is enclosed.				
c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.				
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.				
SEND ALL CORRESPONDENCE TO:				
Brian R. Morrill Biomeasure, Incorporated 27 Maple Street Milford, MA 01757-3650		 SIGNATURE : NAME : Y. Rocky Tsao REGISTRATION NUMBER : 34,053		

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-1-

Lactone Bearing Absorbable PolymersBackground of the Invention

The present invention pertains to biodegradable polymers comprising a lactone, biodegradable compositions comprising the polymer and a therapeutic agent, the use of the compositions for the sustained release of therapeutic agents, wherein the therapeutic agent is reversibly immobilized on the polymer matrix using ionic complexation between the latent carboxylic groups present on the lactone bearing polymer matrix and the cationic group on the therapeutic agent.

In order to overcome the multiple dosing regime associated with therapy involving therapeutic agents, which includes peptides and proteins, having a short *in vivo* half life, numerous technologies are being evaluated for the sustained release of these therapeutic agents. One of these technologies is the encapsulation of drugs in biodegradable matrices such as polyesters, polycarbonates, polyanhydrides, polyorthoesters, polyphosphazenes, polyphosphoesters and the like (see U.S. Patent No. 4,675,189; U.S. Patent No. 4,767,628; U.S. Patent No. 5,271,945; WO 93/20126; GB Patent No. 2,145,422). The biodegradable microparticles containing the therapeutic agent(s) slowly release to maintain an effective plasma level for several days or even for months. The release of the therapeutic agent is dictated by a variety of factors arising from the polymer matrix as well as the physical characteristics of the therapeutic agent, making it possible to engineer the release profile by properly selecting the parameters governing them. The biodegradable polymer matrix degrades *in vivo* to non-toxic metabolites, at rates depending on the chemical nature of the polymer.

However, one of the many problems, encountered during the encapsulation of therapeutic agents in such biodegradable matrices is the inherent incompatibility between the polymer matrix and the therapeutic agent, such as a polypeptide. This incompatibility often leads to poor encapsulation efficiency as manifested during the emulsion solvent evaporation process, described by the oil-in-water process (P. B. O'Donnell and J. W. McGinity in

-2-

Advanced Drug Delivery Reviews, 28(1997), 25-42.). Another consequence of the incompatibility between the polymer matrix and a therapeutic agent, is the formation of phase separated domains inside the microparticle. The release of a therapeutic agent from such a phase separated, non-homogenous system
5 becomes non-predictable. One of the ways to overcome such incompatibility is to anchor the therapeutic agent onto a polymer matrix using reversible bonds such as ionic bonds. These ionic complexes are formed between carboxylic functionalities of the polyester and cationic groups of the therapeutic agent as described in the U.S. Patent No. 5,672,659. The carboxylic acid functionalized
10 polyesters were obtained by the ring opening polymerization of lactones using hydroxycarboxylic acid as an 'initiator', whereby the molecular weight of the resulting polyester is controlled by the molar ratio of the hydroxycarboxylic acid with respect to the monomers. The hydroxy group present in the hydroxycarboxylic acid is expected to participate in the ring opening
15 polymerization, producing telechelic polymers having hydroxy and carboxylic groups at the chain extremities. However, the presence of carboxylic group in the initiator can interfere with the polymerization, as discussed by Zhang et al, in Journal Polymer Science, Polymer Chemistry Ed. 1994, 32,2965.

In this context the teachings of the present invention become relevant.
20 Five membered ring lactones and certain six membered lactones (see review by Johns, D.H. et al., in Ring Opening Polymerization, edited by K.J. Ivin and T. Saegusa, Elsevier Applied Science Publishers, NY) are thermodynamically stable and are considered non-polymerizable under the normal conditions of polymerization described by the present invention. An active hydrogen present
25 on a five membered ring lactone, can be used to initiate the polymerization of other lactones, without affecting the five membered ring lactone. Therefore the five membered ring lactones can be incorporated intact, without unfavorably affecting the polymerization as would have been the case when hydroxy carboxylic acids are used as the initiator. These five membered ring lactones
30 can be selectively used to anchor a therapeutic agent such as a polypeptide either by ionic complexation or by covalent conjugation.

-3-

Hashimoto et al., describe the synthesis of polyurethanes containing glucarodilactones and mannarodilactones by the reaction between the dihydroxy groups present on the dilactone with diisocyanates (Journal of Polymer Science: Part A, Polymer Chemistry 1995, 33, 1495). However, such monomers have 5 never been used in the synthesis of polyesters, polyorthoesters, polyphosphazenes, polycarbonates, polyanhydrides, polyphosphoesters, and the like.

Summary of the Invention

In one aspect, the present invention is directed to a polymer bearing non-10 polymerizable lactone ring wherein the polymer is selected from the group consisting of polyester, polyorthoester, polyphosphoester, polycarbonates, polyanhydrides and polyphosphazenes and copolymers and blends thereof. Depending on the lactone ring starting material that is used to make the polymer bearing non-polymerizable lactone ring, there may be one or multiple lactone 15 rings in the polymer bearing non-polymerizable lactone ring. This is described in more detail below.

The polymer bearing non-polymerizable lactone ring described immediately above can have the non-polymerizable lactone within the polymer chain or the non-polymerizable lactone can be bonded to one or both ends of 20 the polymer chain.

A preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyester. A preferred embodiment of the immediately foregoing polymer is where the polyester is selected from the group consisting of polymers, copolymers or blends of L-lactide, D,L-lactide, D,L-lactide, lactic acid, ε-25 caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol. More preferred is where the polyester is selected from the group consisting of L-lactide, D,L-lactide, glycolide, and polyethylene glycol and the non-polymerizable 30 lactone ring is selected from the group consisting of hydroxybutyrolactone, erythrynlactone, isopropylidene ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone.

-4-

Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyorthoester. A preferred embodiment of the immediately foregoing polymer is where the polyorthoester is obtained from a diketene acetal and a dihydroxy non-polymerizable lactone bearing prepolymer.

5 A preferred embodiment of the immediately foregoing polymer is where the dihydroxy non-polymerizable lactone bearing prepolymer comprises a polyester selected from the group consisting of polymers, copolymers or blends of L-lactide, D,L-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, 10 glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyphosphoester. A preferred embodiment of the immediately foregoing polymer is where the polyphosphoester is obtained from

15 (C₁-C₁₈)alkylphospho-dichloridates, cycloalkylphosphodichloridates or arylphosphodichloridates and a dihydroxy non-polymerizable lactone bearing prepolymer. A preferred embodiment of the immediately foregoing polymer is where the dihydroxy non-polymerizable lactone bearing prepolymer comprises a polyester selected from the group consisting of polymers, copolymers or blends 20 of L-lactide, D,L-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

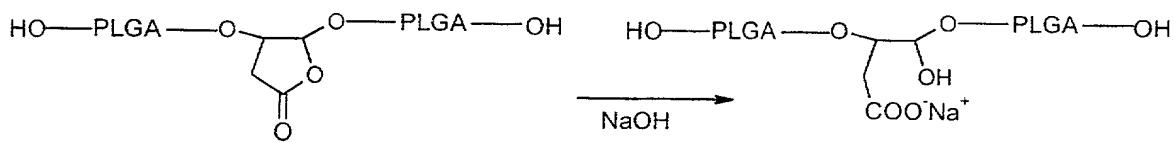
Another preferred polymer bearing non-polymerizable lactone ring is 25 where the polymer is a polycarbonate.

Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyanhydride.

Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyphosphazene. A preferred embodiment of the 30 immediately foregoing polymer is where the polyphosphazene is obtained from poly(dichloro)phosphazene and amino butyrolactone.

-5-

In another aspect, the present invention is directed to a polymer bearing non-polymerizable lactone ring where the polymer is a polyester and wherein the non-polymerizable lactone has been ring opened to its corresponding hydroxycarboxylic acid alkali metal salt. For example, the following scheme 5 shows a polymer bearing a non-polymerizable lactone bearing ring of the present invention before and after ring opening of the lactone ring, it is the ring opened product which is the object of this aspect of the present invention.



10 A preferred embodiment of the immediately foregoing polymer is where the polyester is selected from the group consisting of polymers, copolymers or blends of L-lactide, D,L-lactide, D-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol
15 valerolactone, hydroxyvaleric acid, and butanediol. More preferred is when the polyester is selected from the group consisting of L-lactide, D,L-lactide, glycolide, and polyethylene glycol and the hydroxycarboxylic acid corresponds to the ring opened product of the non-polymerizable lactone ring selected from the group consisting of hydroxybutyrolactone, erythrynlactone, isopropylidene
20 ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone. A most preferred embodiment of the foregoing polymer is where the hydroxycarboxylic acid alkali metal salt is within the polymer chain.

In yet another aspect, the present invention provides a complex comprising a polymer bearing non-polymerizable lactone ring, ionically 25 complexed with a therapeutic agent containing at least one cationic group, wherein the polymer is selected from the group consisting of polyester, polyorthoester, polyphosphoester, polycarbonates, polyanhydrides and polyphosphazenes, and copolymers and blends thereof. A preferred embodiment of the foregoing complex is where the polymer part of the polymer 30 bearing non-polymerizable lactone ring is a polyester and wherein the non-

polymerizable lactone ring has been ring opened to its corresponding hydroxycarboxylic acid alkali metal salt, is ionically complexed with a therapeutic agent containing at least one cationic group. A preferred embodiment of the immediately foregoing polymer is where the polyester is selected from the group consisting of polymers, copolymers or blends of L-lactide, D,L-lactide, D-lactide, lactic acid, ε-caprolactone, hydroxycaprylic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol. More preferred is where the polyester is selected from the group consisting of L-lactide, D,L-lactide, glycolide, and polyethylene glycol and the hydroxycarboxylic acid corresponds to the ring opened product of the non-polymerizable lactone ring selected from the group consisting of hydroxybutyrolactone, erythrynovalactone, isopropylidene ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone. A most preferred embodiment of the foregoing polymer is where the hydroxycarboxylic acid alkali metal salt is within the polymer chain. A further preferred embodiment of the foregoing complex is where the therapeutic agent is selected from the group consisting of LHRH, somatostatin, bombesin/GRP, calcitonin, bradykinins, galanin, MSH, GRF, amylin, tachykinin, secretin, PTH, CGRP, neuromedin, pTHRP, glucagon, neuropeptides, ACTH, PYY, and TSH, or analogues or fragments thereof. An even more preferred embodiment of the foregoing complex is where the therapeutic agent is a somatostatin analogue selected from the group consisting of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂, where the two Cys are bonded by a disulfide bond, N-hydroxyethylpiperazinyl-acetyl-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂ where the two Cys are bonded by a disulfide bond or N-hydroxyethylpiperazinyl-ethylsulfonyl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂ where the two Cys are bonded by a disulfide bond or the therapeutic agent is an LHRH analogue of the formula p-Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH₂.

In still another aspect, the present invention provides a sustained release composition comprising any one of the complexes described hereinabove,

wherein the sustained release composition is in the form of microparticles, microspheres or rods.

In a further aspect, the present invention provides a pharmaceutical composition comprising any one of the complexes or sustained release compositions having an effective amount of the therapeutic agent, described hereinabove and a pharmaceutically-acceptable carrier.

In a yet further aspect, the present invention provides a method of treating or preventing a disease or a condition, which comprises administering any of the pharmaceutical compositions described hereinabove to a patient in need thereof, wherein said disease or condition is a disease or condition that can be treated by the therapeutic agent in the pharmaceutical composition.

In a still further aspect, the present invention provides a method of administering any of the complexes or pharmaceutical compositions described hereinabove to a recipient, wherein the pharmaceutical composition or complex is administered orally, through the nasal passage, through the pulmonary passage or parenterally.

The word "peptide" as used herein encompasses oligopeptides, polypeptides and proteins.

The term "therapeutic agent" encompasses any chemical entity that can be used to treat a disease or condition in a patient in need thereof, and, thus, includes peptides. Preferably the therapeutic agent contains a cationic moiety or can be modified by a cationic moiety, which cationic moiety can be used to form a complex with a polymer of the present invention.

The polymers of the present invention are typically biodegradable agents, that is it disassociates in the biological environment to inert by-products, which are used to complex a therapeutic agent to make a sustained release formulation of the therapeutic agent. This complex, which may be formed into various pharmaceutically-acceptable compositions such as microspheres, microparticles or rods, optionally comprising a pharmaceutically-acceptable carrier, is typically used to provide a sustained delivery of the therapeutic agent to a recipient thereof over a period of time ranging from one day to thirty days.

Detailed Description of the Invention

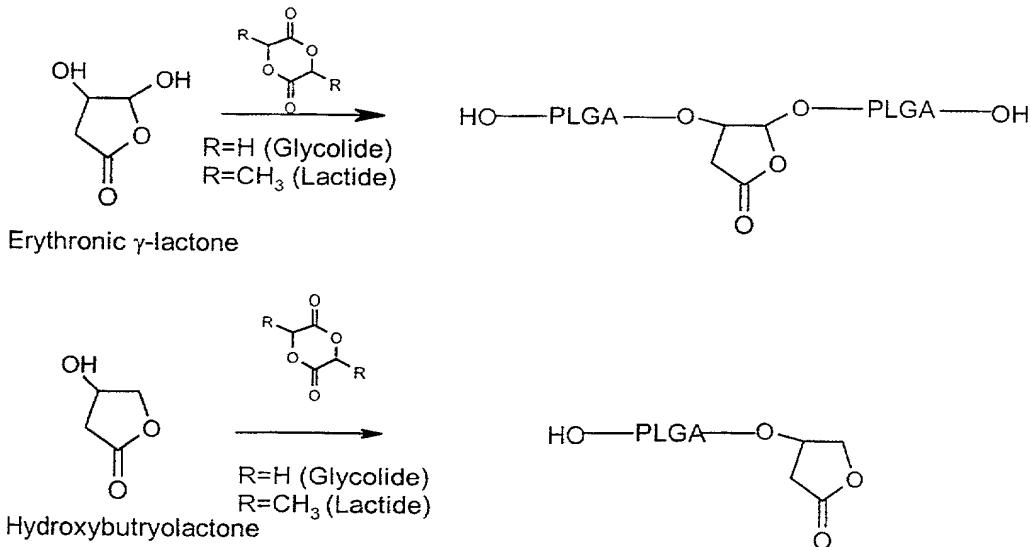
The lactone bearing biodegradable polymers of the invention are tailored to possess the desired chemical reactivity to provide controlled hydrolyzability and exhibit maximum binding capacity to a therapeutic agent having cationic groups, such as a peptide, by the selection of constituent monomers, co-monomers to form chains with predetermined compositions and molecular weights. A lactone bearing biodegradable polymer of this invention comprises a polymer selected from the group consisting of polyesters, polyorthoesters, polyphosphoesters, polycarbonates, polyanhydrides, polyphosphazenes 5 polyoxalates, polyaminoacids, polyhydroxyalkanoates, polyethyleneglycol and copolymers and blends thereof, wherein the foregoing polymers can contain one or more of the following which may be present as polymers, prepolymers or copolymers: L-lactide, D,L-lactide, ϵ -caprolactone, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1,4-dioxepan-2-one, glycolide, ethylene glycol, 10 propylene glycol, and/or butanediol.

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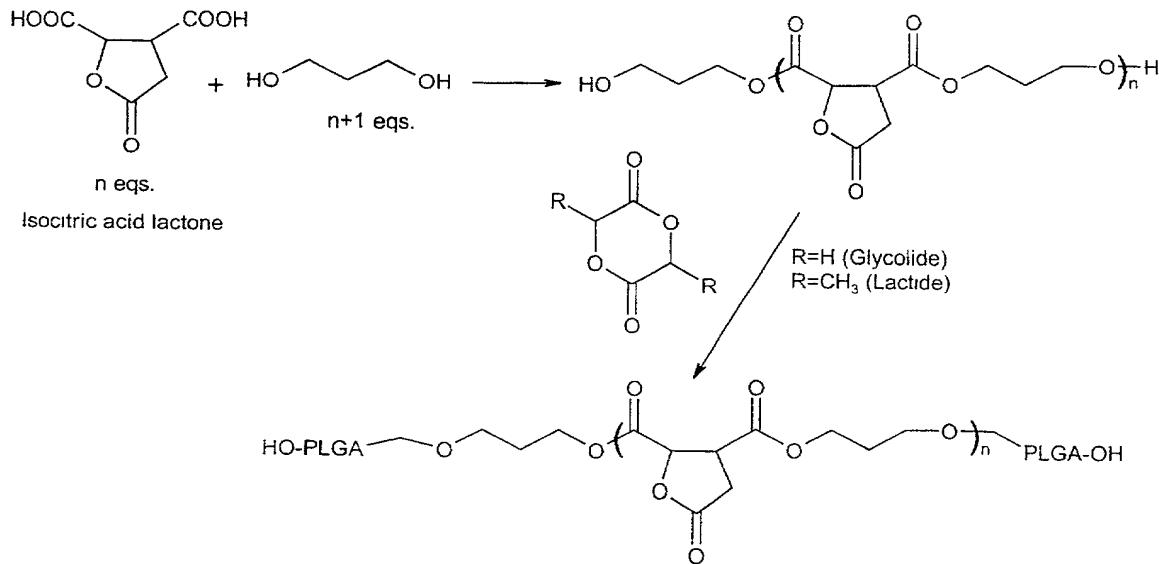
The synthetic strategy employed to prepare compositions of the present invention comprise: synthesis of lactone bearing polymers; synthesis of ionic complexes between the lactone bearing polymer and the biologically active agent such as a peptide; and conversion of the ionic complexes to implants, 20 rods, microspheres or microparticles, which are capable of slowly releasing the therapeutic agent *in vivo*.

Synthesis of lactone bearing polyesters: The lactone bearing polyesters can be synthesized by ring opening polymerization using a hydroxy or amino group present on a non-polymerizable lactone such as butyrolactone. Examples 25 of non-polymerizable five membered lactones having at least one or more active hydrogen containing compound include, but are not limited to hydroxy butyrolactone, aminobutyrolactone, isopropylidene ribonolactone, mannarodilactone, sacharrodilactone, erythronolactone, and the like. The functional group in these non-polymerizable lactone can be used to regulate the 30 ring opening polymerization of monomers or mixtures of monomers such as glycolide, lactide, caprolactone, valerolactone, cyclic carbonates, cyclic anhydrides, oxalates, and the like.

-9-

Scheme 1

Step growth polymerization between appropriate amounts of dicarboxylic acid present on a non-polymerizable five-membered lactone and diol, to obtain 5 (α,ω) dihydroxy oligoester containing non-polymerizable lactone ring could also be used. The dihydroxy functionalities on the oligoester can be used to grow polymer chains to produce high molecular weight polyester, containing non-polymerizable lactone rings.

Scheme 2

-10-

Ring opening polymerization of a lactone or a lactone mixture in the presence of a predetermined concentration of hydroxy or amino groups present on a non-polymerizable lactone as a chain initiator and a catalytic amount of organometallic catalyst, e.g., a mixture of dl-lactide, glycolide and hydroxy butyrolactone, are weighed into a glass reactor in an oxygen free nitrogen filled dry box. Stannous octoate catalyst is added as a solution in toluene. Vacuum is applied to remove the toluene and the reactor is filled with dry argon and left at a positive pressure of argon. The reaction vessel is immersed in an oil bath at a suitable temperature between 120-200°C for polymerization for several hours. At the conclusion of the reaction, vacuum is applied to remove any residual monomer. The reaction vessel is cooled to room temperature and product is collected. The polymer obtained is further purified by dissolving in acetone, and precipitating in ten fold excess cold water. The precipitated polymer is collected by filtration. The product is dried under vacuum at 35°C.

The step growth polymerization which leads to (α,ω)-dihydroxy terminated oligoester containing non-polymerization lactone ring is performed by reacting appropriate amounts of a dicarboxylic acid functionalized lactone and diol, either at room temperature in the presence of coupling agents used in peptide chemistry such as N,N'-dicyclohexylcarbodiimide, N-hydroxybenzotriazole, 2-(1H-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium hexafluoro-phosphate, benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphoniumhexafluorophosphate) or at high temperature wherein the water formed in the reaction is removed by azeotropization with a suitable organic solvent such as benzene, toluene or under a current of N_2 gas.

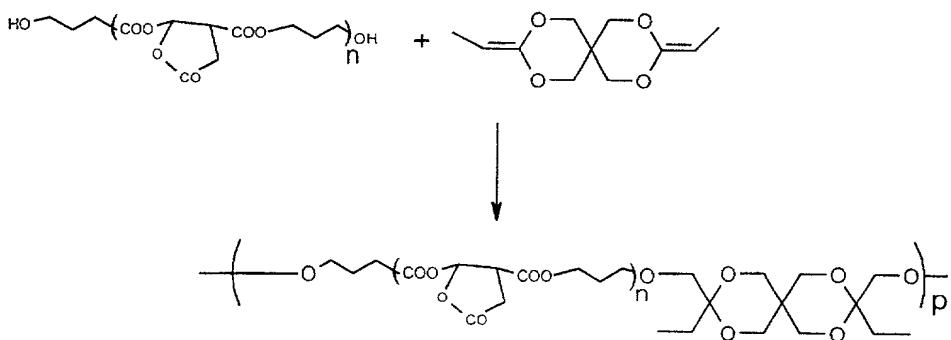
The simplest and the most versatile carboxylic functionalized five membered lactone is isocitric acid lactone, a Kreb's acid which would be metabolized *in vivo*. Examples of diols include simple diols as ethylene glycol, propylene glycol, butanediol, and (α,ω)-dihydroxy terminated oligomers or polymers such as polyethylene glycol, polypropylene glycol, polycaprolactone, polylactides, polyglycolides, polyanhydrides, polyorthoesters, or copolymers thereof. Or a diol may contain non-polymerizable five membered lactone, which may be polycondensed with a dicarboxylic acid. Examples of diols containing

-11-

non-polymerizable lactones include but are not limited to mannolactone, erythrolactone, and the like. Dicarboxylic acids such as adipic, maleic, fumaric, glutaric, tartaric and the like may be used for polycondensation. The polycondensation may be optionally carried out in organic solvents such as dichloromethane, chloroform, tetrahydrofuran, dioxane, dimethylformamide, acetonitrile, dimethylsulfoxide, and the like in the presence of catalysts such as carbodiimide, benzotriazole, thionyl chloride, which are known in the art.

The product of the step growth polymerization may be obtained as a viscous liquid which gels on contact with water, depending on its hydrophilic-lipophilic balance (HLB value). It may be obtained as an amorphous powder by either driving the reaction to completion or by attaching polymer moieties by ring opening polymerization of lactides, glycolides, cyclic carbonates, cyclic anhydrides and the like, used as a mixture or individually to attain the desired properties. The molecular weight of the final polymer can be controlled by choosing the appropriate amount of prepolymer to the monomer. The polymer composition can also be tailored for a desired release profile of the therapeutic agent by appropriate choice of the monomers and molecular weight of the polymer.

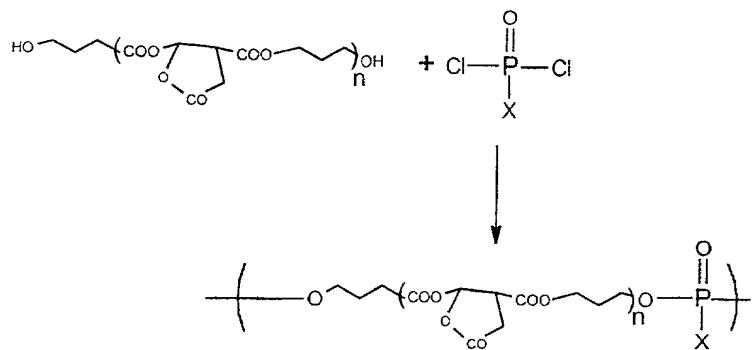
Synthesis of a lactone bearing polymer of the instant invention comprising polyorthoesters can be realized according to the following scheme and substantially according to the procedures taught in Biomaterials, 19 (1998), 791-800, the contents of which are incorporated herein by reference.



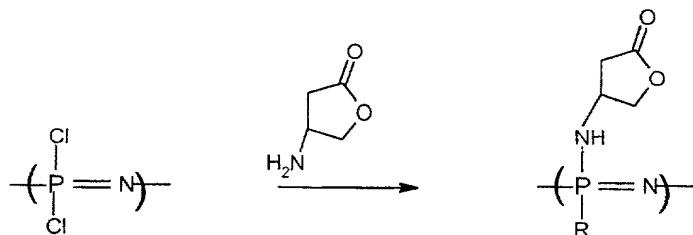
Synthesis of a lactone bearing polymer comprising polyphosphoesters can be accomplished by following the reaction scheme described below, and substantially according to the procedure described in U.S. Patent No. 5,256,765,

-12-

the contents of which are incorporated herein by reference, using a lactone bearing polymer in place of the polymer described therein.



A lactone bearing polymer comprising polyphosphazenes can be
 5 synthesized by the reaction between poly(dichlorophosphazene) and aminobutyrolactone, and substantially according to the procedure described in Chapter 9 of the Handbook of Biodegradable Polymers, edited by A.J. Domb, J. Kost and D.M. Wiseman, Hardwood Academic Publishers, the contents of which are incorporated herein by reference, using a lactone-bearing polymer in place
 10 of the polymer described therein.



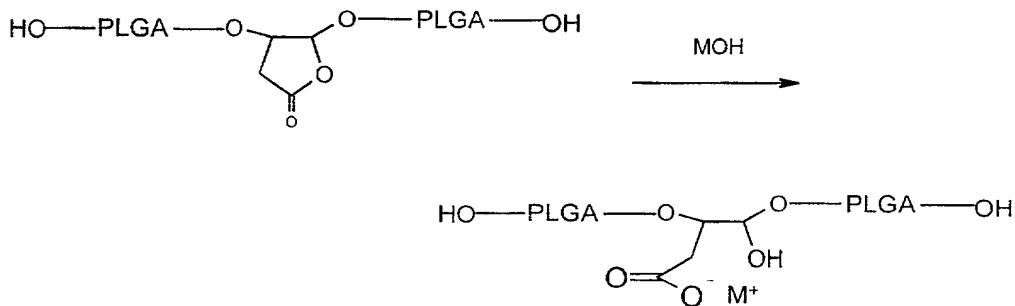
The polymer molecular weight determination is done by Gel Permeation Chromatography (GPC). The system consists of a Waters 6000A solvent delivery system (Waters Corporation, 26 Maple St., Milford, MA 01757),
 15 Dynamax Model AI-3 autoinjector (Ranin, Woburn, MA), Jordi Gel DVB Mixed bed (50x1 cm) column (Jordi Associates, Bellingham, MA) kept at a constant temperature using an Eppendorf CH-460 column heater (Madison, WI), Shimadzu RID-6A detector (Columbia, MD). The data is acquired using a Viscotek Data Manager DM-400 and Viscotek Trisec Software (Viscotek Corporation, Houston, TX). The molecular weights are calculated in comparison
 20

-13-

to a calibration curve constructed using Polystyrene molecular standards purchased from PolySciences, Inc., Warrington, PA.

Synthesis of polymer/peptide ionic complexes from lactone bearing polymer and cationic therapeutic agent:

5 All of the above lactone bearing polymers can be used to prepare ionic complexes with therapeutic agents, such as a peptide, having a cationic moiety. The lactone ring(s) present in these polymers can be opened by an alkali hydroxide to form alkali metal salt of the corresponding hydroxycarboxylic acid. In the case of γ -hydroxycarboxylic acid, it is known that the γ -hydroxycarboxylic
10 acid always reverts back to the more thermodynamically favorable γ -lactone. Therefore, the presence of carboxylic groups in the latent lactone form does not enhance the acidic microenvironment within the polymer. A free acidic group can contribute towards the accelerated degradation of both the polyester and the polypeptide.



15

Examples of the physiologically active peptides that can form a complex with a lactone bearing polymer of the present invention include luteinizing hormone-releasing hormone (sometimes referred to as LHRH, gonadotropin-releasing hormone or Gn-RH), insulin, somatostatin, somatostatin derivative
20 (Sandostatin®; see U.S. Patent Nos. 4,087,390, 4,093,574, 4,100,117 and 4,253,998; Lanreotide®; see U.S. Patent No. 4,853,371), growth hormones (GH), growth hormone-releasing hormones (GH-RH), prolactin, erythropoietin (EPO), adrenocorticotrophic hormone (ACTH), ACTH derivatives (e.g., ebiratide), melanocyte-stimulating hormone (MSH), thyrotropin-releasing hormone
25 (represented by the structural formula (Pyr)Glu-His-ProNH₂, hereinafter also referred to as TRH) and salts and derivatives thereof (see Japanese Patent

-14-

Unexamined Publication Nos. 121273/1975 and 116465/1977), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), vasopressin, vasopressin derivative (desmopressin, see Folia Endocrinologica Japonica, Vol. 54, No. 5, pp. 676-691 (1978), oxytocin, 5 calcitonin, glucagon, gastrin, secretin, pancreozymin, cholecystokinin, angiotensin, human placental lactogen, human chorionic gonadotropin (HCG), enkephalin, enkephalin derivatives (see US Patent No. 4,277,394 and European Patent Publication No. 31567), endorphin, kyotorphin, interferons (e.g., α -, β - and γ -interferons), interleukins (e.g., interleukin 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 10 and 12) tuftsin, thymopoietin, thymosin, thymostimulin, thymic humoral factor (THF), blood thymic factor (FTS) and derivatives thereof (see U.S. Patent No. 4,229,438), tumor necrosis factor (TNF), colony- stimulating factors (e.g., CSF, GCSF, GMCSF, MCSF), motilin, dynorphin, bombesin, neuropeptides, neurotensin, caerulein, bradykinin, atrium sodium-excretion increasing factor, nerve growth factor (NGF), cell growth factors (e.g., EGF, TGF- α , TGF- β , PDGF, acidic FGF, basic FGF), nerve nutrition factors (e.g., NT-3, NT-4, CNTF, GDNF, BDNF), and endothelin-antagonistic peptides and their analogs (see European Patent Publication Nos. 436189, 457195 and 496452, and Japanese Patent Unexamined Publication Nos. 94692/1991 and 130299/1991), a protein derived 15 from α 1 domain of major histocompatibility class I antigen complex (Proceedings of the National Academy of Sciences of the Untied States of America, vol. 91, 9086-9090 (1994) and vol. 94, 11692-11697 (1997)) which has an activity of inhibiting an internalization of insulin receptor, insulin-like growth factor (IGF)-1 receptor, IGF-2 receptor, transferrin receptor, epidermal growth 20 factor receptor, low density lipoprotein (LDL) receptor, macrophage scavenger receptor, GLUT-4 transporter, growth hormone receptor and leptin receptor, and their analogs (derivatives), furthermore their fragments or derivatives thereof. 25

When the physiologically active peptides are salts, the salts include pharmacologically acceptable salts. Examples of the salts are salts formed with inorganic acids (e.g., hydrochloric acid, sulfuric acid, nitric acid and boric acid) or salts formed with organic acids (e.g., carbonic acid, bicarbonic acid, succinic 30

acid, acetic acid, propionic acid and trifluoroacetic acid), when the physiologically active peptide has a basic group such as the amino group.

Examples of specific LHRH analogues that can form a complex with a lactone bearing polymer of the present invention include tryptorelin (p-Glu-His-
5 Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH₂), buserelin ([D-Ser(t-Bu)⁶, des-Gly-NH₂¹⁰]-LHRH(1-9)NHEt), deslorelin ([D-Trp⁶, des-Gly-NH₂¹⁰]-LHRH(1-9)NHEt, fertirelin ([des-Gly-NH₂¹⁰]-LHRH(1-9)NHEt), gosrelin ([D-Ser(t-Bu)⁶, Azgly¹⁰]-LHRH), histrelin ([D-His(Bzl)⁶, des-Gly-NH₂¹⁰]-LHRH(1-9)NHEt), leuprorelin ([D-Leu⁶, des-Gly-NH₂¹⁰]-LHRH(1-9)NHEt), lutrelin ([D-Trp⁶, MeLeu⁷, des-Gly-NH₂¹⁰]-
10 LHRH(1-9)NHEt), nafarelin ([D-Nal⁶]-LHRH and pharmaceutically acceptable salts thereof.

Preferred somatostatin analogs that can form a complex with a lactone bearing polymer of the present invention include those covered by formulae or those specifically recited in the publications set forth below, all of which are
15 incorporated herein by reference:

Van Binst, G. et al. Peptide Research 5:8 (1992);
Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having Antitumor Activity", 22nd European peptide Symposium, September 13-19, 1992, Interlaken, Switzerland;
20 PCT Application WO 91/09056 (1991);
EP Application 0 363 589 A2 (1990);
U.S. Patent No. 4,904,642 (1990);
U.S. Patent No. 4,871,717 (1989);
U.S. Patent No. 4,853,371 (1989);
25 U.S. Patent No. 4,725,577 (1988);
U.S. Patent No. 4,684,620 (1987)
U.S. Patent No. 4,650,787 (1987);
U.S. Patent No. 4,603,120 (1986);
U.S. Patent No. 4,585,755 (1986);
30 EP Application 0 203 031 A2 (1986);
U.S. Patent No. 4,522,813 (1985);
U.S. Patent No. 4,486,415 (1984);

-16-

U.S. Patent No. 4,485,101 (1984);
U.S. Patent No. 4,435,385 (1984);
U.S. Patent No. 4,395,403 (1983);
U.S. Patent No. 4,369,179 (1983);
5 U.S. Patent No. 4,360,516 (1982);
U.S. Patent No. 4,358,439 (1982);
U.S. Patent No. 4,328,214 (1982);
U.S. Patent No. 4,316,890 (1982);
U.S. Patent No. 4,310,518 (1982);
10 U.S. Patent No. 4,291,022 (1981);
U.S. Patent No. 4,238,481 (1980);
U.S. Patent No. 4,235,886 (1980);
U.S. Patent No. 4,224,190 (1980);
U.S. Patent No. 4,211,693 (1980);
15 U.S. Patent No. 4,190,648 (1980);
U.S. Patent No. 4,146,612 (1979);
U.S. Patent No. 4,133,782 (1979);
U.S. Patent No. 5,506,339 (1996);
U.S. Patent No. 4,261,885 (1981);
20 U.S. Patent No. 4,728,638 (1988);
U.S. Patent No. 4,282,143 (1981);
U.S. Patent No. 4,215,039 (1980);
U.S. Patent No. 4,209,426 (1980);
U.S. Patent No. 4,190,575 (1980);
25 EP Patent No. 0 389 180 (1990);
EP Application No. 0 505 680 (1982);
EP Application No. 0 083 305 (1982);
EP Application No. 0 030 920 (1980);
PCT Application No. WO 88/05052 (1988);
30 PCT Application No. WO 90/12811 (1990);
PCT Application No. WO 97/01579 (1997);
PCT Application No. WO 91/18016 (1991);

-17-

U.K. Application No. GB 2,095,261 (1981); and
French Application No. FR 2,522,655 (1983).

Examples of somatostatin analogs that can form a complex with a lactone bearing polymer of the present invention include, but are not limited to,
5 the following somatostatin analogs which are disclosed in the above-cited references:

H-D- β -Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH₂;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys- β -Nal-NH₂;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys- β -Nal-NH₂;

10 H-D- β -Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH₂;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH₂;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;

15 H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH;

H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH;

H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol;

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

20 H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;

H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH₂;

H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;

25 Ac-D-Phe-Lys*-Tyr-D-Trp-Lys-Val-Asp*-Thr-NH₂ (an amide bridge formed between Lys* and Asp*);

Ac-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

Ac-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

30 Ac-D-hArg(Et)₂-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

Ac-L-hArg(Et)₂-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

Ac-D-hArg(CH₂CF₃)₂-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

-18-

Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH₂;
Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;
Ac-L-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;

5 Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NH₂;
Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NHEt;
Ac-hArg(CH₃, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
H-hArg(hexyl₂)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
Ac-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;

10 Ac-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH₂;
Propionyl-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-Thr-NH₂;
Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg(Et)₂-NH₂;
Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
Ac-D-hArg(CH₂CF₃)₂-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-

15 NH₂;
Ac-D-hArg(CH₂CF₃)₂-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-
NH₂;
Ac-D-hArg(Et)₂-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH₂;

20 H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH₂;
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH₂;
H-Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH₂;
H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;

25 H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH₂;
H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
Ac-D-β-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH₂;

30 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH₂;
H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;

-19-

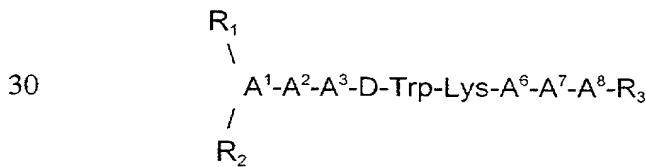
Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
H-D-Phe-Cys-β-Nal-D-Trp-Lys-Val-Cys-Thr-NH₂;
H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH₂;
cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);
5 cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);
cyclo(Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe);
cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe);
cyclo(Pro-Tyr-D-Trp-Lys-Thr-Phe);
cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe);
10 cyclo(Pro-Phe-L-Trp-Lys-Thr-Phe);
cyclo(Pro-Phe-D-Trp(F)-Lys-Thr-Phe);
cyclo(Pro-Phe-Trp(F)-Lys-Thr-Phe);
cyclo(Pro-Phe-D-Trp-Lys-Ser-Phe);
cyclo(Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe);
15 cyclo(D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe);
cyclo(D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe);
cyclo(D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe);
cyclo(D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr);
cyclo(Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);
20 cyclo(Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe);
cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe);
cyclo(N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);
cyclo(Pro-Tyr-D-Trp-4-Amphe-Thr-Phe);
cyclo(Pro-Phe-D-Trp-4-Amphe-Thr-Phe);
25 cyclo(N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe);
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba);
cyclo(Asn-Phe-D-Trp-Lys-Thr-Phe);
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-NH(CH₂)₄CO);
30 cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala);
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH;
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe);

-20-

- cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);
- cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
- cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);
- cyclo(Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba);
- 5 cyclo(Asn-Phe-Phe-D-Trp(NO₂)-Lys-Thr-Phe-Gaba);
- cyclo(Asn-Phe-Phe-Trp(Br)-Lys-Thr-Phe-Gaba);
- cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe(I)-Gaba);
- cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr(But)-Gaba);
- cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH;
- 10 cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH;
- cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-Cys)-OH;
- cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-Cys)-OH;
- cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
- cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba);
- 15 cyclo(Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba);
- cyclo(Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-(CH₂)₃-CO);
- cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
- cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
- cyclo(Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
- 20 H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH₂;
- H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH₂;
- H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH₂; and
- H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH₂.

A disulfide bridge is formed between the two free thiols (e.g., Cys, Pen, 25 or Bmp residues) when they are present in a peptide; however, the disulfide bond is not shown.

Also included are somatostatin agonists of the following formula:



A¹ is a D- or L- isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, β-Nal, β-Pal,

-21-

Trp, Phe, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

A² is Ala, Leu, Ile, Val, Nle, Phe, β -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or

5 NO₂;

A³ is pyridyl-Ala, Trp, Phe, β -Nal, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

A⁶ is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

A⁷ is Ala, Leu, Ile, Val, Nle, Phe, β -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, 10 pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

A⁸ is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe, β -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

15 each R₁ and R₂, independently, is H, lower acyl or lower alkyl; and R₃ is OH or NH₂; provided that at least one of A¹ and A⁸ and one of A² and A⁷ must be an aromatic amino acid; and further provided that A¹, A², A⁷ and A⁸ cannot all be aromatic amino acids.

Examples of linear agonists that can form a complex with a lactone 20 bearing polymer of the present invention include:

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH₂;

H-D-Phe-p-NO₂-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂;

H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂;

H-D-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂;

25 H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂;

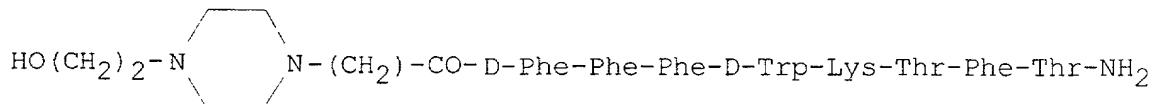
H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂; and

H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala- β -D-Nal-NH₂.

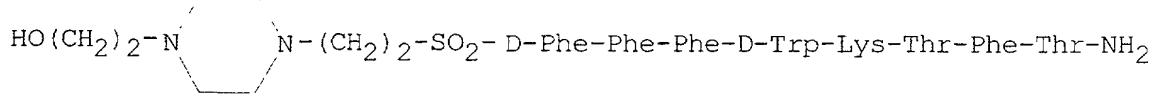
If desired, one or more chemical moieties, e.g., a sugar derivative, mono 30 or poly-hydroxy C₂₋₁₂ alkyl, mono or poly-hydroxy C₂₋₁₂ acyl groups, or a piperazine derivative, can be attached to the somatostatin agonist, e.g., to the N-terminus amino acid. See PCT Application WO 88/02756, European Application 0 329 295, and PCT Application No. WO 94/04752. An example of

-22-

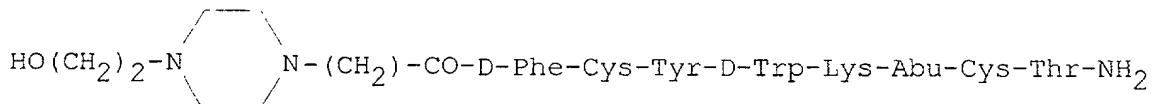
somatostatin agonists which contain N-terminal chemical substitutions are:



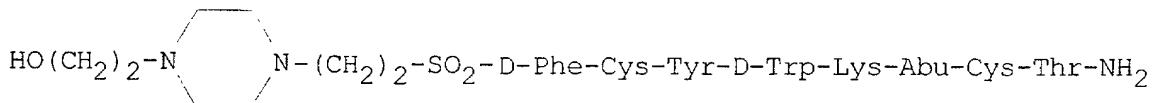
;



5 ;



; and



10

The formation of the ionic complexes is achieved by direct molecular interaction of the components (lactone bearing polymer and therapeutic agent, such as a peptide) in an appropriate solvent with a pretreatment of the lactone bearing polymer with an inorganic base which results in the ring-opened hydroxycarboxylic acid corresponding to the lactone bearing polymer. The

15

lactone bearing polymer is dissolved in a suitable aprotic solvent in a concentration range of 2-25 % (w/v). These organic solvents are either partially or completely miscible with water. Such solvents include acetone, tetrahydrofuran, acetonitrile, ethylene glycol, dimethyl ether, methyl formate, dioxane and the like. To this polymer solution, an aqueous solution of a base

20

such as sodium, potassium or ammonium, calcium, hydroxide or carbonate or bicarbonate, is added to open the intact five membered cyclic lactone, to yield the corresponding metallic salts of hydroxycarboxylic acid. In general, the amount of the inorganic base used corresponds to the amount of counter-anion of the basic peptide.

25

The mixture of the metallic salts of hydroxycarboxylic acid polymer and the inorganic base are stirred and a solution of the therapeutic agent, such as a peptide, in a minimum amount of water either alone or in combination with the

-23-

same organic solvent used for dissolving the peptide, is added. The amount of organic solvent to aqueous in the mixture is adjusted to get a clear solution which is left stirring for 1-2 hours. This solution is precipitated in ice cold water. The precipitate formed is collected by vacuum filtration and dried under vacuum.

5 The peptide content in the formulation is determined by nitrogen analysis performed by QTI, Whitehouse, NJ.

Conversion of ionic complexes to implants, rods, microspheres or microparticles:

The polymer-peptide ionic complexes of this invention can be converted to
10 injectable dosage forms such as implants, rods, microspheres or microparticles by any of the relevant methods described in PCT International Publication Number WO 97/39738, the contents of which are incorporated herein by reference.

The pharmaceutical compositions of this invention can be administered
15 to a patient via administration routes well known to those of ordinary skill in the art, such as parenteral administration, oral administration or topical administration. Preferably, it is administered as a powder or a suspension via intranasal route or as an inhalant through the pulmonary system. When it is administered parenterally it is preferable that it is administered as a dispersion in
20 an isotonic aqueous medium or in a non-aqueous, absorbable gel-forming liquid polyester as described in U.S. Patent No. 5,612,052, the contents of which are incorporated herein by reference. The formulations comprising microparticles of the present invention can also include a variety of optional components. Such components include, but are not limited to, surfactants, viscosity controlling
25 agents, medicinal agents, cell growth modulators, dyes, complexing agents, antioxidants, other polymers such as carboxymethyl cellulose, gums such as guar gum, waxes/oils such as castor oil, glycerol, dibutyl phthalate and di(2-ethylhexyl)phthalate as well as many others. If used, such optional components comprise from about 0.1% to about 20%, preferably from about 0.5% to about
30 5% of the total formulation.

Compositions or formulations of this invention can be used to treat a disease or condition in a patient in need thereof according to the use that is

-24-

known for the therapeutic agent, such as a peptide or peptides, which is in the composition, which are known to one of ordinary skill in the art. For example, microparticles of the present invention comprising a somatostatin analogue will be useful in treating a disease or condition that can be treated with somatostatin
5 or an analogue thereof.

The effective dosages of a composition or formulation of the present invention to be administered to a patient can be determined by the attending physician or veterinarian and will be dependent upon the proper dosages contemplated for the therapeutic agent and the quantity of the therapeutic agent
10 in the composition. Such dosages will either be known or can be determined by one of ordinary skill in the art without undue experimentation.

The following examples illustrate the present invention and are not to be construed to limit the scope of the present invention.

Example 1

15 Ring Opening Polymerization: Synthesis of 65/35 p(dl-lactide-co-glycolide) initiated by erythrynlactone:

DL-Lactide (43.8g, 0.3041M), glycolide (17.6g, 1517M), erythrynlactone (1g, 0.0084M) and 0.2ml stannous octoate catalyst were added to the reaction vessel provided with a mechanical stirrer. The reaction vessel was evacuated
20 and purged with dry argon at least three times and then left at a positive pressure of argon. The reaction vessel was immersed in an oil bath kept at about 160°C. The reaction was allowed to proceed for about 6 hours. After completion of the reaction, the temperature was lowered to about 100°C and the vessel was evacuated to remove any residual monomer. The reaction vessel
25 was cooled to room temperature, quenched in liquid N₂ and the polymer was collected. The polymer was further purified by preparing a 10% solution and precipitating in cold water. The precipitate was collected and dried under vacuum. Polymer molecular weight determined by GPC analysis is Mn= 7250, Mw=12700

Example 2

30 Ring opening polymerization: synthesis of p(dl-lactide) initiated by isopropylidene ribonolactone:

-25-

DL-Lactide (60g, 0.4166M) and isopropylidene ribonolactone (2.35g, 0.0125M) were polymerized according to the procedure described in Example 1. The molecular weights of the polymer obtained determined by GPC analysis is Mn=5050, Mw=7980.

5

Example 3

Step growth polymerization and subsequent ring opening polymerization:
Preparation of polyethylene glycol-co-poly(lactide-co-glycolide) copolymers containing butyrolactone

Isocitric acid (Aldrich Chemicals, St. Louis, MO) (2.5g, .0143M) and polyethylene glycol-400 were mixed in a three necked round bottom flask, along with 50ml of toluene. The toluene was refluxed at about 130°C to azeotropically remove the water formed during the reaction by using a Dean-Stark apparatus. After about 48h, the toluene was completely removed by distillation, and DL-lactide (30g, 0.2082M), and glycolide (16.1g, 0.1388M) were added along with 15 0.2ml stannous octoate catalyst in toluene. The temperature of the reaction vessel was raised to about 160°C and the polymerization was carried out for about 6h. At the end of the polymerization, the reaction vessel was evacuated to remove any residual monomer.

20

Example 4

Step growth polymerization and subsequent ring opening polymerization:

Isocitric acid lactone (2.5g, 0.0143M) and propanediol (1.202g, 0.0157M) were mixed and reacted at about 90°C, under refluxing benzene. The water formed was removed by azeotropization with a Dean-Stark trap. The reaction was allowed to proceed overnight, after which benzene was removed by 25 distillation to yield a viscous liquid which solidifies on cooling.

30

The reaction vessel was transferred to a dry-box and 25.2g of dl-lactide and 7.25g of glycolide were added along with 0.2ml stannous octoate solution in toluene. The reaction vessel was purged with dry argon and the polymerization was performed at about 160°C for about 8h. The polymer was quenched in liquid N₂, collected and dissolved in acetone and precipitated in cold water. The filtered polymer was dried under vacuum at about 40°C. Mn= 3790, Mw= 7040, as determined by GPC.

-26-

Example 5

Synthesis of ionic complexes of polymer synthesized in Example 4 and Lanreotide® using 1N NaOH as the base:

One gram of polymer dissolved in acetone was treated with 0.45ml 1N
5 NaOH. The solution was stirred for about 20 min, and 0.29g of Lanreotide®
(Kinerton, Ltd., Dublin, Ireland; Lanreotide has the formula: H-β-D-Nal-Cys-Tyr-
D-Trp-Lys-Val-Cys-Thr-NH₂ where the two Cys are bonded by a disulfide bond),
dissolved in 2ml of 1:1 acetone/water was added to the polymer solution. The
polymer solution was left stirring for about 2h, and then it was precipitated in
10 cold water. The product was filtered and vacuum dried. The peptide content in
the formulation determined by nitrogen analysis was 17.6%.

Example 6

Synthesis of ionic complexes of the polymer synthesized in Example 4 and Lanreotide® using NaHCO₃ as the base:

15 One gram of the polymer made in Example 4 dissolved in acetone was treated with 0.45ml of 1N NaHCO₃. The solution was stirred for about 20min, and 0.29g of Lanreotide® dissolved in 2ml of 1:1 acetone/water was added to the polymer solution. The polymer solution was left stirring for about 2h, and it was precipitated in cold water. The product was filtered and vacuum dried. The
20 peptide content in the formulation determined by nitrogen analysis was 17.6%.

Example 7

In vivo testing of the samples prepared in Examples 5 and 6:

Samples from Examples 5 & 6 were each separately ground and sieved with a mortar and pestle, and sieved using a 125 micron sieve. Rats were
25 administered 6.75mg of peptide equivalent per rat, using an injection medium consisting of 2% carboxymethylcellulose, 1% Tween 20® (Aldrich Chemicals, St. Louis, MO) and saline. Blood samples were collected at various time intervals and the plasma Lanreotide® levels were determined by radioimmuno assay. The plasma Lanreotide® levels (ng/ml) for the two samples tested are
30 shown in Table I below.

-27-

TABLE I

Sample/Time	6h	Day 2	Day 8	Day 15	Day 22
Example 5	21.7± 4.5	30.3±2.7	30.2±7.5	0.8±0.3	0.05±0.02
Example 6	24.4±5.2	31.4±5.8	20.8±7.2	1.4±1.2	0.141±0.09

CLAIMS

What is claimed is:

1. A polymer bearing non-polymerizable lactone ring wherein the polymer is selected from the group consisting of polyester, polyorthoester, 5 polyphosphoester, polycarbonates, polyanhydrides and polyphosphazenes and copolymers and blends thereof.
2. A polymer bearing non-polymerizable lactone ring according to claim 1 wherein the non-polymerizable lactone ring is within the polymer chain or the non-polymerizable lactone ring is bonded to one or both ends of the polymer 10 chain.
3. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyester.
4. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyorthoester.
- 15 5. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyphosphoester.
6. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polycarbonate.
7. A polymer bearing non-polymerizable lactone ring according to 20 claim 2, wherein the polymer is a polyanhydride.
8. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyphosphazene.
9. A polymer bearing non-polymerizable lactone ring according to claim 3, wherein the polyester is selected from the group consisting of polymers, 25 copolymers or blends of l-lactide, dl-lactide, d-lactide, lactic acid, ε-caprolactone, hydroxycaprylic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.
10. A polymer bearing non-polymerizable lactone ring according to 30 claim 9, wherein the polyester is selected from the group consisting of l-lactide, dl-lactide, glycolide, and polyethylene glycol and the non-polymerizable lactone ring is selected from the group consisting of hydroxybutyrolactone,

erythrynlactone, isopropylidene ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone.

11. A polymer bearing non-polymerizable lactone ring according to claim 4, wherein the polyorthoester is obtained from a diketene acetal and a dihydroxy non-polymerizable lactone ring bearing prepolymer.

12. A polymer bearing non-polymerizable lactone ring according to claim 11 wherein the dihydroxy non-polymerizable lactone ring bearing prepolymer comprises a polyester selected from the group consisting of polymers, copolymers or blends of L-lactide, D,L-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

13. A polymer bearing non-polymerizable lactone ring according to claim 5, wherein the polyphosphoester is obtained from (C₁-C₁₈)alkylphosphodichlorides, cycloalkylphosphodichlorides or arylphosphodichlorides and a dihydroxy non-polymerizable lactone ring bearing prepolymer.

14. A polymer bearing non-polymerizable lactone ring according to claim 13 wherein the dihydroxy non-polymerizable lactone ring bearing prepolymer contains a polyester selected from the group consisting of polymers, copolymers or blends of L-lactide, D,L-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

15. A polymer bearing non-polymerizable lactone ring according to claim 8, wherein the polyphosphazene is obtained from poly(dichloro)phosphazene and amino butyrolactone.

16. A polymer bearing non-polymerizable lactone ring according to claim 10, wherein the non-polymerizable lactone ring has been ring opened to its corresponding hydroxycarboxylic acid alkali metal salt.

-30-

17. A polymer bearing non-polymerizable lactone ring according to claim 16, wherein the hydroxycarboxylic acid alkali metal salt is within the polymer chain.

18. A complex comprising a polymer bearing non-polymerizable lactone ring according to claim 1, ionically complexed with a therapeutic agent containing at least one cationic group.

19. A complex comprising a polymer bearing non-polymerizable lactone ring according to claim 17, ionically complexed with a therapeutic agent containing at least one cationic group.

10 20. A complex according to claim 19, wherein the therapeutic agent is selected from the group consisting of LHRH, somatostatin, bombesin/GRP, calcitonin, bradykinins, galanin, MSH, GRF, amylin, tachykinin, secretin, PTH, CGRP, neuromedin, pTHRP, glucagon, neuropeptides, ACTH, PYY, PYY, and TSH, or an analogue or fragment thereof.

15 21. A complex according to claim 20, wherein the therapeutic agent is a somatostatin analogue selected from the group consisting of H- β -D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂, where the two Cys are bonded by a disulfide bond, N-hydroxyethylpiperazinyl-acetyl-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂ where the two Cys are bonded by a disulfide bond or N-20 hydroxyethylpiperazinyl-ethylsulfonyl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂ where the two Cys are bonded by a disulfide bond.

22. A complex according to claim 20, wherein the therapeutic agent is an LHRH analogue of the formula p-Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH₂.

25 23. A sustained release composition comprising a complex according to claim 21 wherein the composition is in the form of microparticles, microspheres or rods.

30 24. A sustained release composition comprising a complex according to claim 22 wherein the composition is in the form of microparticles, microspheres or rods.

-31-

25. A pharmaceutical composition comprising a sustained release composition according to claim 23 having an effective amount of the therapeutic agent and a pharmaceutically-acceptable carrier.

5 26. A pharmaceutical composition comprising a sustained release composition according to claim 24 having an effective amount of the therapeutic agent and a pharmaceutically-acceptable carrier.

10 27. A method of treating or preventing a disease or a condition, which comprises administering a pharmaceutical composition according to claim 25 to a patient in need thereof, wherein said disease or condition is a disease or condition that can be treated by the therapeutic agent in the pharmaceutical composition.

15 28. A method of treating or preventing a disease or a condition, which comprises administering a pharmaceutical composition according to claim 26 to a patient in need thereof, wherein said disease or condition is a disease or condition that can be treated by the therapeutic agent in the pharmaceutical composition.

20 29. A method of administering a pharmaceutical composition according to claim 25 to a recipient, wherein said pharmaceutical composition is administered orally, through the nasal passage, through the pulmonary passage or parenterally.

30. A method of administering a pharmaceutical composition according to claim 26 to a recipient, wherein said pharmaceutical composition is administered orally, through the nasal passage, through the pulmonary passage or parenterally.



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(71) Applicant (for all designated States except US):	BIOMEASURE INCORPORATED [US/US]; 27 Maple Street, Milford, MA 01757-3650 (US).		
(72) Inventor; and			
(73) Inventor/Applicant (for US only):	IGNATIOUS, Francis, X. [IN/US]; 15 Eagle Rock Drive, Milville, MA 01529 (US).		
(74) Agents:	TSAO, Y., Rocky et al.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2805 (US).		

(54) Title: LACTONE BEARING ABSORBABLE POLYMERS

(57) Abstract

The present invention pertains to biodegradable polymers comprising a non-polymerizable lactone, biodegradable compositions comprising the polymer and a therapeutic agent, the use of the compositions for the sustained release of therapeutic agents, wherein the therapeutic agent is reversibly immobilized on the polymer matrix using ionic complexation between the latent carboxylic groups present on the lactone bearing polymer matrix and a cationic group on the therapeutic agent.

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled LACTONE BEARING ABSORBABLE POLYMERS, the specification of which:

is attached hereto.

was filed on May 2, 2001 as Application Serial No. 09/830,945 and was amended on _____.

was described and claimed in PCT International Application No. PCT/ US99/25706 filed on November 2, 1999 and as amended under PCT Article 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §119(e)(1) of any United States provisional application(s) listed below:

U.S. Serial No.	Filing Date	Status
60/106,708	November 2, 1998	

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status
09/184,413	11/02/1998	Abandoned
09/428,709	10/28/1999	Abandoned

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
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Combined Declaration and Power of Attorney

Page 2 of 2 Pages

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Y. Rocky Tsao, Reg. No. 34,053; Brian R. Morrill Reg. No. 42,098; Alan F. Feeney Reg. No. 43,609; Timothy A. French, Reg. No. 30,175; Eric L. Prahl, Reg. No. 32,590; and Frank R. Occhiali, Reg. No. 35,306.

Address all telephone calls to Brian R. Morrill at telephone number (508) 478-0144.

Address all correspondence to Brian R. Morrill, Esq. at:

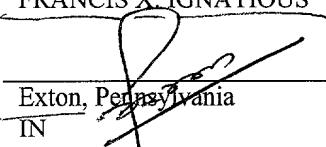
Biomeasure, Incorporated
27 Maple Street
Milford, MA 01757

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1-00
Full Name of Inventor: FRANCIS X. IGNATIOUS

Date: June 11, 2001

PA

Inventor's Signature: 
Residence Address: Exton, Pennsylvania
Citizenship: IN
Post Office Address: 606 Sylvania Road
Exton, Pennsylvania 19341
United States of America